I. Katona

Arthritis Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research

December 1, 1998

Town Center Hotel
8727 Colesville Road, Silver Spring, MD

NDA 20-998, Celebrex ™, (celecoxib), Searle

Contents

Agenda and Questions

Arthritis Advisory Committee

December 1, 1998

NDA 20-998 Celebrex™ (celecoxib) Searle

Volume I: FDA Medical Reviews

Osteoarthritis

Statistical Review

STATISTICAL REVIEW AND EVALUATION

DRAFT

NDA: 20-998/1P
Applicant: G.D. Searle & Co.
Name of Drug: Celebrex™ (Celecoxib) Capsules
Route of Administration: Oral
Documents Reviewed: NDA 20-998: Vol. 1.1-1.3, 1.129-1.131, 1.150-257, 1.422-441 (Total Vol. : 1.1-1.452) (submitted June 30, 1998)
Indication: Treatment of Osteoarthritis
Related INDs: 48,395; 52,153; 52,613; 53,125; 53,734
Medical Officers: James Witter, MD (HFD-550) (Osteoarthritis)
Lawrence Goldkind MD (HFD-180) (Gastrointestinal)

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1. Background

Celecoxib (SC-58635) is a novel compound that selectively inhibits cyclooxygenase 2 (COX-2), the inducible form of the enzyme cyclooxygenase (also known as prostaglandin G/H synthase). Celecoxib is an oral anti-inflammatory and analgesic agent developed for treating the signs and symptoms of Osteoarthritis (OA) and rheumatoid arthritis (RA) and for the management of pain. All these three indications were submitted under this NDA 20-998.

OA is primarily a disease of altered cartilage metabolism of multifactorial etiology. Prevalence parallels age, with the disease being more common in women than in men. Synovial inflammation may be present in advanced disease and can occur early in variants of OA. Prominent signs and symptoms include articular pain, stiffness and functional impairment. OA of the knee and hip are associated with disability, particularly with respect to ambulation, although degenerative changes of the spine, hands and feet also lead to functional limitation. In patients with OA, mechanical stress leads to altered cartilage metabolism and eventually disruption of matrix integrity. Microfractures and erosions are the result, leading to eventual disruption and loss of articular cartilage. This loss produces a disruption of joint architecture which results in subarticular cysts, bony sclerosis, and osteophyte formation. The disruption of joint architecture typically produces pain with joint loading. Joint instability may also result. Stiffness, though common, is not prominent and may result from synovial involvement. Because mechanical stress is a principle component in the pathophysiology of OA, the disease typically occurs in weight-bearing joints.

This reviewer reviewed the indication of treatment of osteoarthritis. For this indication, the sponsor submitted eleven studies, which included five pivotal, five supportive, and one long-term safety study which were conducted in patients with OA to provide evidence of the efficacy of celecoxib for the

Table 1.6. WOMAC Osteoarthritis Index

How much pain do you have?
- walking on a flat surface
- going up or down stairs
- at night while in bed
- sitting or lying
- standing upright

Amount of joint stiffness
- How severe is your stiffness after first awakening in the morning?
- How severe is your stiffness after sitting, lying, or resting later in the day?

Ability to move around and to look after yourself - What degree of difficulty did you have with:

- descending stairs	- getting in/out of car	- getting in/out of bath
- ascending stairs	- going shopping	- sitting
- rising from sitting	- putting on socks/stockings	- getting on/off toilet
- standing	- taking off socks/stockings	- heavy domestic duties
- bending to floor	- rising from bed	- light domestic duties
- walking on flat surface	- lying in bed	

Score: 0=none, 1=mild, 2=moderate, 3=severe, and 4=extreme

The Incidence of and Time to Withdrawal Due to Lack of Arthritis Efficacy (treatment failure) are presented for all pivotal studies. Time to Withdrawal Due to Lack of Arthritis Efficacy was calculated as the difference between the last dose date and the first dose date plus one day. Patients who completed the study according to the protocol or withdrew for reasons other than lack of arthritis efficacy were censored at the final study visit or at the withdrawal time, respectively.

The APS Pain Measure consisted of five questions as shown in Table 1.7. The first question required a yes or no response. The remaining questions required rating the pain and its interference with daily activities on a scale of 0 (no pain) to 10 (worst pain possible). Patients completed the APS Pain Measure at Baseline and daily thereafter for the first seven days of dosing with study medication.

Table 1.7. APS Pain Scale

	Question	Scale
1	Have you experienced any pain in the past 24 hours?	yes/no
2	How much pain are you having right now?	0-10
3	Indicate the worst pain you have had in the past 24 hours.	0-10
4	Indicate the average level of pain you have had in the past 24 hours	0-10
5	Indicate how pain has interfered with you in:	
	• General Activity	0-10
	• Mood	0-10
	• Walking Ability	0-10
	• Relations with other People	0-10
	• Sleep	0-10
	• Normal Work, Including Housework	0-10
	• Enjoyment of Life	0-10

The reasons for early termination are listed in Tables 1.8 and 1.9.

Table 1.8. Reasons for Study Termination (All Randomized Patients: 12-Week Pivotal Studies 020, 021, and 054)

	Number of Osteoarthritis Patients by Treatment Group				
		Celecoxib			Naproxen
Study	Placebo	50 mg BID	100 mg BID	200 mg BID	500 mg BID
Study 020	**(n=204)**	**(n=203)**	**(n=197)**	**(n=202)**	**(n=198)**
Total Completed	**91 (45%)**	**118 (58%)**	**116 (59%)**	**129 (64%)**	**116 (59%)**
Total Withdrawn	**113 (55%)**	**85 (42%)**	**81 (41%)**	**73 (36%)**	**82 (41%)**
Lost to Follow-up	3 (1%)	1 (<1%)	3 (2%)	1 (<1%)	3 (2%)
Pre-Existing Violation	3 (1%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Protocol Non-Compliance	12 (6%)	4 (2%)	7 (4%)	2 (<1%)	8 (4%)
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)
Adverse Event	16 (8%)	18 (9%)	31 (16%)	21 (10%)	18 (9%)
Study 021	**(n=242)**	**(n=252)**	**(n=240 [b])**	**(n=233)**	**(n=226)**
Total Completed	**119 (49%)**	**168 (67%)**	**165 (69%)**	**154 (66%)**	**147 (65%)**
Total Withdrawn	**123 (51%)**	**84 (33%)**	**75 [b] (31%)**	**79 (34%)**	**79 (35%)**
Lost to Follow-up	5 (2%)	1 (<1%)	0 (0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Protocol Non-Compliance	13 (5%)	8 (3%)	7 (3%)	4 (2%)	8 (4%)
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)
Adverse Event	14 (6%)	16 (6%)	16 (7%)	23 (10%)	30 (13%)
Study 054	**(n=218)**	**(n=216)**	**(n=207)**	**(n=213)**	**(n=207)**
Total Completed	**79 (36%)**	**111 (51%)**	**111 (54%)**	**119 (56%)**	**118 (57%)**
Total Withdrawn	**139 (64%)**	**105 (49%)**	**96 (46%)**	**94 (44%)**	**89 (43%)**
Lost to Follow-up	2 (<1%)	4 (2%)	0 (0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	1 (<1%)
Protocol Non-Compliance	5 (2%)	6 (3%)	8 (4%)	9 (4%)	7 (3%)
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)
Adverse Event	16 (7%)	17 (8%)	27 (13%)	25 (12%)	29 (14%)

Table 1.9. Reasons for Study Termination (All Randomized Patients: 6-Week Pivotal Studies 060 and 087)

	Number of Osteoarthritis Patients by Treatment Group		
		Celecoxib	
Study	**Placebo**	**100 mg BID**	**200 mg QD**
Study 060	**(n=232)**	**(n=231)**	**(n=223)**
Total Completed	**146 (63%)**	**194 (84%)**	**182 (82%)**
Total Withdrawn	**86 (37%)**	**37 (16%)**	**41 (18%)**
Lost to Follow-up	2 (<1%)	4 (2%)	2 (<1%)
Pre-Existing Violation	2 (<1%)	2 (<1%)	2 (<1%)
Protocol Non-Compliance	6 (3%)	2 (<1%)	7 (3%)
Treatment Failure	56 (24%)	18 (8%)	21 (9%)
Adverse Event	20 (9%)	11 (5%)	9 (4%)
Study 087	**(n=244)**	**(n=243)**	**(n=231)**
Total Completed	**164 (67%)**	**194 (80%)**	**191 (83%)**
Total Withdrawn	**80 (33%)**	**49 (20%)**	**40 (17%)**
Lost to Follow-up	1 (<1%)	0 (0%)	1 (<1%)
Pre-Existing Violation	4 (2%)	6 (2%)	4 (2%)
Protocol Non-Compliance	8 (3%)	7 (3%)	5 (2%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 (5%)	9 (4%)	6 (3%)

Table 1.10. Number of OA Patients Who Completed or Withdrew from the GI endoscopy Studies (Randomized Patients: Supportive Studies 062, and 071)

	Number of Osteoarthritis Patients by Treatment Group			
	Celecoxib	Naproxen	Diclofenac	Ibuprofen
Study	**200 mg BID**	**500 mg BID**	**75 mg BID**	**800 mg TID**
Study 062	**(n=194)**	**(n=195)**	—	—
Total Completed	150 (77%)	105 (54%)	—	—
Total Withdrawn	44 (23%)	90 (46%)	—	—
Study 071	**(n=272)**	—	**(n=285)**	**(n=255)**
Total Completed	220 (81%)	—	207 (73%)	167 (65%)
Total Withdrawn	52 (19%)	—	78 (27%)	88 (35%)

2. Efficacy Analysis

2.1 Intent-To-Treat Patients

A patient will be included in the Intent-to-Treat Cohort if he or she is randomized to treatment and has taken at least one dose of study medication.

2.2 Efficacy Variables:

In the study protocols for the OA studies, the endpoints originally designated primary were: Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Arthritis Pain - VAS, and Physician's Global Assessment of Arthritic Condition. The per protocol secondary measures of arthritis efficacy were Functional Capacity Classification, WOMAC OA Index, Incidence of Withdrawal Due to Lack of

Arthritis Efficacy, Time to Withdrawal Due to Lack of Arthritis Efficacy, Osteoarthritis Severity Index (OASI), APS Pain Measure, Patient Assessment of Function, and SF-36 Health Survey. At the 12 February 1998 pre-NDA meeting, the Division of Anti-inflammatory, Analgesics and Ophthalmic Drug Products (HFD-550), requested modification of the primary and secondary efficacy variables. The principal change was the inclusion of the WOMAC OA Index as a primary measure of efficacy although it was not prospectively defined as a primary endpoint in the OA studies.

The final list of retrospectively defined **primary OA efficacy endpoints** included the following:

- Patient's Global Assessment of Arthritic Condition
- Patient's Assessment of Arthritis Pain - VAS
- Physician's Global Assessment of Arthritic Condition
- WOMAC OA Index (Composite score and subscores for pain, joint stiffness, and physical function)

The final list of **secondary OA efficacy endpoints** included the following:

- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- APS Pain Measure

The remaining measures,

- Functional Capacity Classification
- OASI (OA severity index)
- SF-36 Health Survey

were designated **supporting** data.

Primary treatment comparisons (celecoxib 200mg vs placebo and celecoxib 100 mg vs placebo) for primary efficacy variables were defined. Multiplicity adjustments were made for the primary treatment comparisons with Hochberg's step-up procedure to control the family-wise Type-I error at the level of 0.05. Mean change analyses (studies with a flared Baseline) or mean score analyses (studies without a flared Baseline) using analysis of covariance (ANCOVA) models were performed for Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Arthritis Pain, Physician's Global Assessment of Arthritic Condition, WOMAC Osteoarthritis Index, Functional Capacity Classification, Osteoarthritis Severity Index, Quality of Life SF-36 Heath Survey, APS Pain Measures, and Patient Assessment of Function. For Patient's a and Physician's Global Assessments, patients were classified as 'Improved', 'No Change' or 'Worsened' based on a two-grade change criterion.

Carrying forward the last efficacy measurement will impute the efficacy measurements that are missing.

Multiple Comparison Adjustment

In each study, multiplicity adjustments were made for the primary treatment comparisons with Hochberg's step-up procedure to control the family-wise Type-I error at the level of 0.05. To perform this

treatment of the signs and symptoms of OA. The pivotal studies were all double-blind, placebo-controlled trials of at least six weeks duration, in which 200 or more patients per treatment were enrolled.

1.1 Study Design :

Table 1.1. Summary of Clinical Studies Conducted in Patients with OA: 12-Week Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-020 R: N49-98-06-020 Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Knee	72 Investigators U.S. and Canada 5 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-021 R: N49-98-06-021 Celecoxib Comparative Efficacy and UGI Safety vs Naproxen in OA of the Knee	80 Investigators U.S. and Canada 26 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-054 R: N49-98-06-054 Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Hip	125 Investigators U.S. and Canada 9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo

Table 1.2. Summary of Clinical Studies Conducted in Patients with OA: 6-Week Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-060 R: N49-98-06-060 QD vs BID Efficacy in OA of the Knee	51 Investigators United States 29 May 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo
P: N49-98-02-087 R: N49-98-06-087 QD vs BID Efficacy in OA of the Knee	101 Investigators United States 28 Jan 1998	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo

Table 1.3. Summary of Clinical Studies Conducted in Patients with OA: Placebo-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-047 R: N49-97-06-047 Dose-ranging Efficacy in OA	26 Investigators United States 9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (4 Weeks)	Celecoxib 25 mg BID, 100 mg BID or 400 mg BID or Placebo
P: N49-96-02-013 R: N49-96-16-013 Pilot Efficacy in OA	26 Investigators United States 26 Jan 1996	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (2 Weeks)	Celecoxib 40 mg BID, 100 mg BID or 200 mg BID or Placebo

Table 1.4. Summary of Clinical Studies Conducted in Patients with OA: Active-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: I49-96-02-042 R: I49-98-06-042 Ex-U.S. OA Trial	129 Investigators 20 countries in Australia, Europe and South Africa 2 Dec 1996	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Diclofenac 50 mg BID
P: N49-97-02-062 R: N49-98-06-062 Comparative Incidence of UGI Ulcers: Celecoxib vs Naproxen in Patients with OA and RA	75 Investigators in United States 13 May 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200 mg BID or Naproxen 500 mg BID
P: N49-97-02-071 R: N49-98-06-071 Comparative Incidence of UGI Ulcers: Celecoxib vs Diclofenac and Ibuprofen in Patients with OA and RA	121 Investigators in United Sates 21 Jul 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200mg BID or Diclofenac 75 mg BID or Ibuprofen 800 mg TID

1.2 Study Population and Design - Placebo-Controlled Studies

In order to be entered into a placebo-controlled OA trial, patients had to have been diagnosed according to the American College of Rheumatology (ACR) criteria for OA of the knee or hip . OA of the knee was defined as knee pain and radiologic evidence of OA (defined as the presence of osteophytes) plus at least one of the following three:

1. Age > 50 years;
2. Stiffness < 30 minutes;
3. Crepitus.

OA of the hip was defined as hip pain plus at least two of the following three:

1. Erythrocyte sedimentation rate (ESR, Westergren method) less than 20 mm/hour;
2. Radiographic evidence of femoral or acetabular osteophytes;
3. Radiographic evidence of joint space narrowing (superior, axial or medial).

Patients were to be in an OA flare at the Baseline Visit. The criteria for demonstrating OA flare depended on whether the patient was in Category 1 (i.e., currently receiving NSAID or analgesic therapy for his/her OA) or Category 2 (i.e., not receiving NSAID or analgesic therapy and had uncontrolled OA).

For patients in Category 1, an OA flare was demonstrated if both the Baseline Patient's and the Physician's Global Assessment of Arthritic Condition were rated as "fair," "poor" or "very poor" **and** the Baseline arthritis assessments met at least three of the following four criteria:

1. Patient's Assessment of Arthritis Pain (VAS) measurement of at least 40 mm;
2. An increase of two or more points in the OA Severity Index from the screening assessment;

3. An increase from the screening visit of one or more grades in the Patient's Global Assessment of Arthritic Condition;
4. An increase from the screening visit of one or more grades in the Physician's Global Assessment of Arthritic Condition.

For patients in Category 2, an OA flare was demonstrated if they met at least three of the following four criteria during the Baseline arthritis assessments:

1. Patient's Assessment of Arthritis Pain (VAS) measurement of at least 40 mm;
2. The OA Severity Index was ≥7;
3. The Patient's Global Assessment of Arthritic Condition was "poor" or "very poor";
4. The Physician's Global Assessment of Arthritic Condition was "poor" or "very poor."

In addition, patients in these studies were to have a Functional Capacity Classification (46) of I-III at Baseline as described by the following criteria:

Class	Description
I	Complete functional capacity with ability to carry on all usual duties without handicaps
II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self care
IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self care

Each of the three 12-week pivotal studies (Studies 020, 021, and 054) was a randomized, multicenter, double-blind, active- and placebo-controlled comparison study of the efficacy and safety of celecoxib 50 mg BID, 100 mg BID, and 200 mg BID and naproxen 500 mg BID in patients with OA of the knee (Studies 020 and 021) or hip (Study 054). Each study was comprised of a Screening Period, a Baseline Visit, and a 12-week Treatment Period. The Screening Visit occurred 2 to 14 days prior to the administration of the first dose of study medication, at which time each patient gave a medical history, underwent a physical examination, and had clinical laboratory tests performed. Following completion of the Screening Assessments, patients taking NSAIDs or analgesics were instructed to discontinue current NSAID or analgesic use and notify the Investigator when flare symptoms began. In Study 021, Baseline and Week 12 endoscopies were also performed.

Patients satisfying the arthritis flare criteria returned to the study site for a Baseline Visit where the SF-36 Health Survey and WOMAC Osteoarthritis Index were completed and the following Baseline arthritis assessments were performed: Patient's and Physician's Global Assessment of Arthritic Condition, OA Severity Index, and Functional Capacity Classification. In addition, patients were asked to identify the joint with the most severe OA symptoms, either right knee or left knee (Studies 020 and 021) or right hip or left hip (Study 054). This joint was identified as the "Index Joint." Patients assessed the amount of arthritis pain in the "Index Joint" using a 100 mm VAS between 0 (no pain) and 100 (very severe pain). Patients were issued American Pain Society (APS) Pain Measure and Patient Assessment of Function

questionnaires to be completed at Baseline and every evening for the first seven days of the study. Patients were instructed to return the questionnaires to the study site at the Week 2 Visit.

The arthritis assessments were repeated at the Week 2, Week 6, and Week 12 Visits. The SF-36 Health Survey and WOMAC Osteoarthritis Index were repeated at the Week 2 and Week 12 Visits. In addition, at each of the follow-up visits, adverse effects were assessed, selected clinical laboratory tests were performed, and information on concomitant medications was collected. Patients who withdrew before the end of the study had all final assessments performed at the time of withdrawal (Early Termination Visit).

The two 6-week pivotal studies (Studies 060 and 087) were conducted to confirm whether a once-a-day dose regimen was appropriate and were both randomized, parallel group, multicenter, double-blind, placebo-controlled studies comparing the efficacy of celecoxib 200 mg QD to celecoxib 100 mg BID in patients with OA of the knee. These studies were each comprised of a Screening Period, a Baseline Visit, and a six-week Treatment Period. The Screening Visit occurred 2 to 14 days prior to the administration of the first dose of study medication and was identical to the Screening Visit performed in the 12-week pivotal studies. Patients satisfying the arthritis flare criteria returned to the study site for a Baseline Visit. With the exception of the APS Pain Measure and Patient Assessment of Function, arthritis assessments performed were identical to those in the 12-week pivotal studies. The arthritis assessments were repeated at Week 2 and Week 6 Visits. The SF-36 Health Survey (Study 060 only) and WOMAC Osteoarthritis Index were repeated at the Week 6 Visit. In addition, at each of the follow-up visits, adverse effects were assessed, selected clinical laboratory tests were performed, and information on concomitant medications was collected. Patients who withdrew before the end of the study had all final assessments performed at the time of withdrawal (Early Termination Visit).

1.3 Description of the Scales Used for Measurement of OA Efficacy

The Patient's and Physician's Global Assessments of Arthritic Condition were made independently and were graded according to the scale in Table 1.5.

Table 1.5. Scale for Patient's and Physician's Global Assessments of Arthritic Condition

Grade	Assessment
1	Very good, asymptomatic and no limitation of normal activities
2	Good, mild symptoms and no limitation of normal activities
3	Fair, moderate symptoms and limitation of some normal activities
4	Poor, severe symptoms and inability to carry out most normal activities
5	Very poor, very severe symptoms that are intolerable; inability to carry out all normal activities

The Patient's Assessment of Arthritis Pain (VAS) was used for patient-identified "Index Joints". Patients assessed the amount of arthritis pain in the "Index Joint" on a 100 mm line (Visual Analog Scale) with the 0 mm point indicating no pain and 100 mm point indicating very severe pain.

The WOMAC Osteoarthritis Index is a tri-dimensional, self-administered questionnaire. The patient responded to 24 component items: five regarding pain, two regarding stiffness, and 17 regarding physical function. The questionnaire is listed in Table 1.6.

procedure, the p-values for the two primary treatment comparisons were ordered. First, the largest p-value was compared with the value of 0.05. If this value is ≤ 0.05, then both treatment groups were claimed to be significant, or else, the smaller p-value was compared with the value of 0.025. If the smaller p-value is ≤ 0.025, the treatment corresponding to this p-values was claimed to be significant, or else, no treatment was claimed to significant.

Four primary variables were defined in each Phase III pivotal study. To claim a celecoxib treatment group to be significantly better than placebo, WOMAC and two of the three remaining primary variables must be statistically significant against placebo with Hochberg's step-up procedure applied to the primary comparisons for each variable.

2.3 Study N49-96-02-020

STUDY OBJECTIVES

Primary Objectives
The primary objectives of this study were to:
1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks with placebo in treating the signs and symptoms of OA of the knee; and
2. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the knee.

Secondary Objectives
The secondary objectives of this study were to:
1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

Study Design

This randomized, double-blind, placebo-controlled, parallel group, multicenter study is designed to compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID versus naproxen 500 mg BID in treating the signs and symptoms of osteoarthritis (OA) of the knee. In addition, the safety of SC-58635 50 mg, 100 mg, and 200 mg administered BID will be evaluated. Patients with OA of the knee that is in a flare state and with a Functional Capacity Classification of I-III, who have not received any non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics within two days (within four days for patients receiving oxaprozin or piroxicam) before the Baseline Arthritis Assessments, are eligible for study participation.

Patients were randomized to receive either SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The duration of treatment was 12 weeks with follow-up visits two, six and 12 weeks after the first dose of study medication. The planned sample size for this trial was 200 patients per treatment group.

Analysis results

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.1.

Primary variables:

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.2, A.9) and Physician's Global Assessment of Arthritic Condition (Tables A.3, A.10), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.4), WOMAC scores (Tables A.5-A.8), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

Secondary variables:

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, SC-58635 200 mg BID doses compared to placebo (Table A.11). The SC-58635 100 mg BID, and SC-58635 200 mg BID groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.12). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were mostly not statistically significant ($p>0.05$).

For the mean change in APS pain score from baseline, the SC-58635 100 mg BID and SC-58635 200 mg BID groups were statistically superior to placebo on day 2-7 ($p<0.05$) (Table A.13). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ($p>0.05$) (Table A.13).

Supportive variables:

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ($p<0.05$) for SC-58635 100 mg BID at Weeks 2 and 12 and for SC-58635 200 mg BID at all timepoints as compared to placebo (Table A.14). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg BID groups compared to placebo at Weeks 2, 6, and 12 (Table A.15). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Study N49-96-02-021

STUDY OBJECTIVES

Primary Objectives
The primary objectives of this study were to:

1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with placebo in treating the signs and symptoms of OA of the knee;
2. Evaluate the UGI safety of SC-58635 50 mg, 100 mg, and 200 mg BID versus naproxen 500 mg BID and placebo in patients with OA of the knee; and
3. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the knee.

Secondary Objectives
The secondary objectives of this study were to:
1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

Study Design
This was a double-blind, placebo-controlled, multicenter, parallel group comparison of the efficacy and UGI safety of SC-58635 versus placebo and naproxen in patients with OA of the knee. The study consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug, and at Week 2, Week 6, and Week 12 following the first dose of study drug. The UGI safety of SC-58635 was assessed with endoscopies performed at Baseline and Week 12 (or Early Termination) and testing was done for Helicobacter pylori (H. pylori) at Baseline and Week 12 (or Early Termination) Visit. Patients who met the inclusion criteria (see below) were randomly assigned to receive SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The duration of treatment was 12 weeks.

The planned sample size for this trial was 200 patients per treatment group.

Analysis results

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.16.

Primary variables:

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.17, A.24) and Physician's Global Assessment of Arthritic Condition (Tables A.18, A.25), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.19), WOMAC scores (Tables A.20-A.23), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

Secondary variables:

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg BID, compared to placebo (Table A.26). The SC-58635 100 mg BID, and SC-58635 200 mg BID groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.27). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ($p>0.05$).

For the mean change in APS pain score from baseline, the SC-58635 100 mg BID and SC-58635 200 mg BID groups were statistically superior to placebo on day 2-7 ($p<0.05$) (Table A.28). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ($p>0.05$) (Table A.28).

Supportive variables:

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ($p<0.05$) for SC-58635 100 mg BID and SC-58635 200 mg BID at all timepoints as compared to placebo (Table A.29). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg BID groups compared to placebo at Weeks 2, 6, and 12 (Table A.30). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Study N49-98-06-054

STUDY OBJECTIVES

Primary Objectives

The primary objectives of this study were to:

1. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks with placebo in treating the signs and symptoms of OA of the hip; and
2. Evaluate the safety of SC-58635 50 mg, 100 mg, and 200 mg BID for 12 weeks in patients with OA of the hip.

Secondary Objectives

The secondary objectives of this study were to:

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the hip; and
2. Compare the efficacy of SC-58635 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the hip.

Study Design

This is a double-blind, randomized, placebo-controlled, multicenter, parallel group study comparing the efficacy of SC-58635 versus naproxen in patients with OA of the hip. The planned sample size for this trial was 200 patients per treatment group.

Analysis results

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.31.

Primary variables:

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.32, A.38) and Physician's Global Assessment of Arthritic Condition (Tables A.33, A.39), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.34), WOMAC scores (Tables A.35-A.37), SC-58635 100 mg BID and SC-58635 200 mg BID were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and naproxen 500 mg BID for each primary efficacy assessment at most visits.

Secondary variables:

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg BID, compared to placebo (Table A.40). The SC-58635 100 mg BID, and SC-58635 200 mg BID groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.41). The differences between the SC-58635 100 mg BID and SC-58635 200 mg BID groups and the naproxan group were not statistically significant ($p>0.05$).

For the mean change in APS pain score from baseline, the SC-58635 100 mg BID and SC-58635 200 mg BID groups were statistically superior to placebo on days 1-7 ($p<0.05$) (Table A.42). The differences between the SC-58635 200 mg BID group and the naproxan group were not statistically significant ($p>0.05$). The naproxan group was statistically superior to the SC-58635 100 mg BID group on days 4-7 (Table A.42).

Supportive variables:

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ($p<0.05$) for SC-58635 100 mg BID and SC-58635 200 mg BID at weeks 6 and 12 as compared to placebo (Table A.43). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg BID groups compared to placebo at Weeks 2, 6, and 12 (Table A.44). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Reviewer's Comment: In Studies N49-96-02-020, N49-96-02-021and N49-98-06-054, the SC-58635 100 mg BID, and SC-58635 200 mg BID groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, SC-58635 200 mg BID groups, and the naproxan group. These results were supported by the analyses of the secondary and the supportive variables.

Study N49-98-06-060

STUDY OBJECTIVES

Primary Objective
The primary objective of this study was to compare the efficacy of SC-58635 200 mg QD and SC-58635 100 mg BID with placebo in treating the signs and symptoms of OA of the knee.

Secondary Objectives
The secondary objectives of this study were to:
1. Compare the efficacy of SC-58635 200 mg QD with SC-58635 100 mg BID in treating the signs and symptoms of OA of the knee; and
2. Assess the safety of SC-58635 200 mg taken QD for six weeks and SC-58635 100 mg taken BID for six weeks in patients with OA of the knee.

Study Design
This is a double-blind, randomized, placebo-controlled, multicenter, parallel group study comparing the efficacy of SC-58635 versus placebo in treating the signs and symptoms of OA of the knee.

Intent-to-Treat Patients

A patient will be included in the Intent-to-Treat Cohort if he or she has OA of the knee and the knee is identified as the index joint, is randomized to treatment and has taken at least one dose of study medication.

Analysis results

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.45.

Primary variables:

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.46, A.50) and Physician's Global Assessment of Arthritic Condition (Tables A.47, A.51), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.48), WOMAC scores (Tables A.49), SC-58635 100 mg BID and SC-58635 200 mg QD were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID and SC-58635 200 mg QD for each primary efficacy assessment.

Secondary variables:

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg QD, compared to placebo (Table A.52). The SC-58635 100 mg BID, and SC-58635 200 mg QD groups were statistically significantly different from placebo

with regard to time to withdrawal due to lack of arthritis efficacy (Table A.53). The differences between the SC-58635 100 mg BID and SC-58635 200 mg QD groups were not statistically significant ($p>0.05$).

Supportive variables:

The mean changes from Baseline in the Functional Capacity Classification were statistically significantly greater ($p<0.05$) for SC-58635 100 mg BID and SC-58635 200 mg QD at week 2, as compared to placebo (Table A.54). At week 6, the mean changes from Baseline in the Functional Capacity Classification were numerically, but not statistically significantly greater ($p>0.05$) for SC-58635 100 mg BID and SC-58635 200 mg QD, as compared to placebo (Table A.54). Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg QD groups compared to placebo at Weeks 2, and 6 (Table A.55). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Study N49-98-02-087

STUDY OBJECTIVES

Primary Objective
The primary objective of this study was to compare the efficacy of SC-58635 200 mg QD and SC-58635 100 mg BID with placebo in treating the signs and symptoms of OA of the knee.

Secondary Objectives
The secondary objectives of this study were to:
1. Compare the efficacy of SC-58635 200 mg QD with SC-58635 100 mg BID in treating the signs and symptoms of OA of the knee; and
2. Assess the safety of SC-58635 200 mg taken QD for six weeks and SC-58635 100 mg taken BID for six weeks in patients with OA of the knee.

Study Design

This is a double-blind, randomized, placebo-controlled, multicenter, parallel group study comparing the efficacy of SC-58635 versus placebo in treating the signs and symptoms of OA of the knee.

Intent-to-Treat Patients

A patient will be included in the Intent-to-Treat Cohort if he or she has OA of the knee and the knee is identified as the index joint, is randomized to treatment and has taken at least one dose of study medication.

Analysis results

The tables of the analysis results are presented in the appendix.

The patient disposition is listed in Table A.56.

Primary variables:

For the primary efficacy variables: the mean and categorical change from baseline of the scores of Patient's Global Assessment of Arthritic Condition, (Tables A.56, A.60) and Physician's Global Assessment of Arthritic Condition (Tables A.57, A.61), the mean change from baseline of Patient's Assessment of Pain (VAS) (Table A.58), WOMAC scores (Tables A.59), SC-58635 100 mg BID and SC-58635 200 mg QD were statistically superior to placebo at all visits based on an adjustment for multiplicity using Hochberg's step-up procedure. There were no statistically significant differences between SC-58635 100 mg BID and SC-58635 200 mg QD for each primary efficacy assessment.

Secondary variables:

The number of patients withdrawing due to lack of efficacy was statistically significantly lower for the SC-58635 100 mg BID, and SC-58635 200 mg QD, compared to placebo (Table A.62). The SC-58635 100 mg BID, and SC-58635 200 mg QD groups were statistically significantly different from placebo with regard to time to withdrawal due to lack of arthritis efficacy (Table A.63). The differences between the SC-58635 100 mg BID and SC-58635 200 mg QD groups were not statistically significant ($p>0.05$).

Supportive variables:

The mean changes from Baseline in the Functional Capacity Classification were numerically greater for SC-58635 100 mg BID and SC-58635 200 mg QD at all visits, as compared to placebo (Table A.64), but the differences were mostly not statistically significant. Results of the Osteoarthritis Severity Index demonstrated statistically significant improvement for SC-58635 100 mg BID and SC-58635 200 mg QD groups compared to placebo at Weeks 2, and 6 (Table A.65). There were no statistically significant differences between the two SC-58635 treatment groups for this variable.

Reviewer's Comment: : In Studies N49-98-06-060 and N49-98-02-087, the SC-58635 100 mg BID, and SC-58635 200 mg QD groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, and SC-58635 200 mg QD groups. These results were supported by the analyses of the secondary and the supportive variables.

3. GI analysis

Study N49-96-02-021

Study Design

This was a double-blind, placebo-controlled, multicenter, parallel group comparison of the efficacy and UGI safety of SC-58635 versus placebo and naproxen in patients with OA of the knee. The study consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug, and at Week 2, Week 6, and Week 12 following the first dose of study drug. The UGI safety of SC-58635 was assessed with endoscopies performed at Baseline and Week 12 (or Early Termination) and testing was done for Helicobacter pylori (H. pylori) at Baseline and Week 12 (or Early Termination) Visit. Patients who met the inclusion criteria were randomly assigned to receive SC-58635 50 mg BID, SC-58635 100 mg BID, SC-58635 200 mg BID, naproxen 500 mg BID, or placebo. The duration of treatment was 12 weeks.

A UGI endoscopic examination was performed within seven days prior to the first dose of study medication. The mucosa of the stomach and the duodenum were each assigned a separate score using the scale shown in the following table. Erythema was not included in the mucosal scoring scale.

Mucosal Scoring Scale

Grade	Description
0	No visible lesions (i.e., normal mucosa
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions*
5	11-25 erosions*
6	>25 erosions*
7	Ulcer**

* An erosion was defined as any break in the mucosa without depth
** An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

Patient Populations Analyzed - Endoscopy Analysis

Intent-to-Treat (ITT) Cohort- Endoscopy Analysis

The ITT Cohort included all patients who were randomized to treatment and had taken at least one dose of study medication.

Evaluation of UGI Endoscopy Results

Crude ulcer rate (score=7) at Week 12 (or Final Visit) were analyzed with CMH tests. For each patient there were three possible outcome categories: known ulcer, known no ulcer and unknown. Last observation carried forward (LOCF) was used for the known ulcer outcome only.

UGI ENDOSCOPY RESULTS

The number of gastroduodenal ulcers (i.e., a gastric or duodenal score of seven) in each treatment group was determined by endoscopy performed at Baseline and Week 12 (or Early Termination). Observed counts of gastroduodenal ulcer by treatment group and observation timepoint are presented in Table 3.1. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates are presented in Table 3.2. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 4 (4%) placebo patients, 8 (5%) SC-58635 50 mg BID patients, 7 (5%) SC-58635 100 mg BID patients, 13 (9%) SC-58635 200 mg BID patients and 34 (23%) naproxen 500 mg BID patients (Table 3.2). Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with the other

treatment groups ($p<0.001$). There was no difference over the 12 weeks of the study in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p \geq 0.173$). Also, there was no difference in the incidence of ulcers among the SC-58635 groups ($p \geq 0.204$) (Table 3.2). These results were confirmed by analyses of the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow up endoscopy). Based on this analysis 5 (2%) placebo patients, 8 (3%) SC-58635 50 mg BID patients, 7 (3%) SC-58635 100 mg BID patients, 13 (6%) SC-58635 200 mg BID patients and 34 (16%) naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in the naproxen 500 mg BID group compared with all other treatment groups ($p<0.001$) and there were no differences between placebo and any of the SC-58635 groups ($p \geq 0.073$). Further, there was no difference in the incidence of ulceration between any of the SC-58635 groups ($p \geq 0.168$) (Table 3.2).

TABLE 3.1 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 96- 02- 021
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL
ITT - KNEE AND HIP PATIENTS

	PLACEBO (N=247)		SC-58635 50MG BID (N=258)		SC-58635 100MG BID (N=239)		SC-58635 200MG BID (N=237)		NAPROXEN 500MG BID (N=233)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	63	1	30	2	30	1	25	2	19	2
WK 6 (29-76)	37	1	32	3	34	3	40	2	34	10
WK 12(77-91)	102	2	156	3	148	3	137	9	112	22
>91	10	1	7	0	8	0	6	0	11	0
TOTAL	212	5	225	8	220	7	208	13	176	34

TABLE 3.2 GASTRODUODENAL ENDOSCOPY RESULTS (a)- N49- 96- 02- 021
ANALYSIS OF CRUDE ULCER RATE
ITT - KNEE AND HIP PATIENTS

	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN 500MG BID	OVERALL p-VALUE(c)
	(N=247)	(N=258)	(N=239)	(N=237)	(N=233)	
WEEK 12						
CRUDE ULCER RATE(a):						<0.001
NO ULCER	102(96%)	156(95%)	148(95%)	137(91%)	112(77%)	
ULCER	4(4%)	8(5%)	7(5%)	13(9%)	34(23%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/62)	84(20/64)	87(22/65)	87(34/53)	
FINAL						
CRUDE ULCER RATE(b):						<0.001
NO ULCER	212(98%)	225(97%)	220(97%)	208(94%)	176(84%)	
ULCER	5(2%)	8(3%)	7(3%)	13(6%)	34(16%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(30/0)	25(25/0)	12(12/0)	16(16/0)	23(23/0)	

p-VALUES FOR TREATMENT COMPARISONS(d):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 12:	0.781	0.173	0.644	0.992	0.204	0.233	<0.001	<0.001	<0.001	<0.001
FINAL:	0.642	0.073	0.472	0.903	0.168	0.221	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;
Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
'd) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis

Observed counts of gastric ulcer by treatment group and observation timepoint are presented in Table 3.3. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.4. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 4 (4%) placebo patients, 8 (5%) SC-58635 50 mg BID patients, 7 (5%) SC-58636 100 mg BID patients, 10 (7%) SC-58635 200 mg BID patients and 25 (18%) naproxen 500 mg BID patients. Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with all other treatment groups ($p \leq 0.004$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p \geq 0.375$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.529$). The trend in crude erosion/ulcer rate was similar to that of the crude ulcer rate with the pairwise comparisons showing no statistically significant differences between the placebo and SC-58635 groups ($p \geq 0.459$) or between the SC-58635 dose groups ($p \geq 0.191$) and finding statistically significant differences between the naproxen group and all other treatment groups including placebo ($p<0.001$) (Table 3.4). These results were confirmed by analyses of crude ulcer and erosion/ulcer rates for the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow-up endoscopy). Based on this analysis 5 (2%) placebo patients, 8 (3%) SC-58635 50 mg BID patients, 7 (3%) SC-58635 100 mg BID patients, 10 (5%) SC-58635 200 mg BID patients and 25 (12%) naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in naproxen 500 mg BID compared with all other treatment ($p<0.005$) and there were no differences between placebo and any SC-58635 groups ($p \geq 0.210$). Further, there was no difference in the incidence of ulceration between any of the SC-58635 groups ($p \geq 0.489$) (Table 3.4).

TABLE 3.3 GASTRIC ENDOSCOPY RESULTS-- N49- 96- 02- 021
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL
ITT - KNEE AND HIP PATIENTS

	PLACEBO		SC-58635 50MG BID		SC-58635 100MG BID		SC-58635 200MG BID		NAPROXEN 500MG BID	
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	63	1	30	2	30	1	26	1	19	2
WK 6 (29-76)	37	1	32	3	34	3	41	1	39	5
WK 12 (77-91)	102	2	156	3	148	3	138	8	116	18
>91	10	1	7	0	8	0	6	0	11	0
TOTAL	212	5	225	8	220	7	211	10	185	25

TABLE 3.4 GASTRIC ENDOSCOPY RESULTS (a)- N49- 96- 02- 021
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE
ITT - KNEE AND HIP PATIENTS

	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN 500MG BID	OVERALL p-VALUE(d)
	(N=247)	(N=258)	(N=239)	(N=237)	(N=233)	
WEEK 12						
CRUDE ULCER RATE(a):						<0.001
NO ULCER	102(96%)	156(95%)	148(95%)	138(93%)	116(82%)	
ULCER	4(4%)	8(5%)	7(5%)	10(7%)	25(18%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/62)	84(20/64)	89(22/67)	92(34/58)	
CRUDE EROSION/ULCER RATE:						<0.001
NO EROSION/ULCER	76(72%)	127(77%)	111(72%)	106(72%)	51(36%)	
EROSION/ULCER (c)	30(28%)	37(23%)	44(28%)	42(28%)	90(64%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/62)	84(20/64)	89(22/67)	92(34/58)	
FINAL						
CRUDE ULCER RATE(b):						<0.001
NO ULCER	212(98%)	225(97%)	220(97%)	211(95%)	185(88%)	
ULCER	5(2%)	8(3%)	7(3%)	10(5%)	25(12%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(30/0)	25(25/0)	12(12/0)	16(16/0)	23(23/0)	
CRUDE EROSION/ULCER	RATE:					<0.001
NO EROSION/ULCER	160(74%)	178(76%)	165(73%)	167(76%)	89(42%)	
EROSION/ULCER (c)	57(26%)	55(24%)	62(27%)	54(24%)	121(58%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(30/0)	25(25/0)	12(12/0)	16(16/0)	23(23/0)	

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 12										
ULCER RATE:	0.801	0.375	0.658	0.981	0.593	0.529	<0.001	<0.001	<0.001	0.004
EROSION/ ULCER RATE:	0.756	0.912	0.459	0.191	0.521	0.598	<0.001	<0.001	<0.001	<0.001
FINAL										
ULCER RATE:	0.657	0.210	0.503	0.893	0.509	0.489	<0.001	<0.001	<0.001	0.005
EROSION/ ULCER RATE:	0.573	0.774	0.773	0.336	0.947	0.411	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;
Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Erosion/ Ulcer is defined as an endoscopy score equal to 3,4,5,6,7
(d) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
(e) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis

Observed counts of duodenal ulcer by treatment group and observation timepoint are presented in Table 3.5. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.6. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 3 (2%) SC-58635 200 mg BID patients and 11 (8%) naproxen 500 mg BID patients. No ulcers were reported in patients in the placebo, SC-58635 50 mg BID, and SC-58635 100 mg BID treatment groups. Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with all other treatment groups ($p \leq 0.012$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p>0.218$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.079$). The trend in crude erosion/ulcer rate was similar to that of the crude ulcer rate with the pairwise comparisons showing no statistically significant differences between the placebo and SC-58635 groups ($p \geq 0.487$) or between the SC-58635 dose groups ($p \geq 0.320$) and finding statistically significant differences between the naproxen group and all other treatment groups including

placebo ($p<0.001$) (Table 3.6). These results were confirmed by analyses of crude ulcer and erosion/ulcer rates for the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow-up endoscopy). Based on this analysis 3 (1%) SC-58635 200 mg BID patients and 11 (5%) naproxen 500 mg BID patients developed an ulcer. There were no ulcers in the placebo, or SC-58635 50 mg BID or 100 mg BID groups. The incidence of ulceration was significantly greater in naproxen 500 mg BID compared with all other treatment ($p<0.016$) and there were no differences between placebo and any SC-58635 treatment groups ($p \geq 0.106$). Further, there was no difference in the incidence of ulceration between any of the SC-58635 treatment groups ($p \geq 0.098$) (Table 3.6).

TABLE 3.5 DUODENAL ENDOSCOPY RESULTS -- N49- 96- 02- 021
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL
ITT - KNEE AND HIP PATIENTS

	PLACEBO		SC-58635		SC-58635		SC-58635		NAPROXEN	
			50MG BID		100MG BID		200MG BID		500MG BID	
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	64	0	32	0	31	0	26	1	20	1
WK 6 (29-76)	38	0	35	0	37	0	41	1	39	5
WK 12 (77-91)	104	0	158	0	151	0	145	1	129	5
>91	11	0	7	0	8	0	6	0	11	0
TOTAL	217	0	232	0	227	0	218	3	199	11

TABLE 3.6 DUODENAL ENDOSCOPY RESULTS (a)- N49- 96- 02- 021
DUODENAL ENDOSCOPY RESULTS (a)
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE
ITT - KNEE AND HIP PATIENTS

	PLACEBO	SC-58635	SC-58635	SC-58635	NAPROXEN	
		50MG BID	100MG BID	200MG BID	500MG BID	OVERALL
	(N=247)	(N=258)	(N=239)	(N=237)	(N=233)	p-VALUE(d)
WEEK 12						
CRUDE ULCER RATE(a):						<0.001
NO ULCER	104(100%)	158(100%)	151(100%)	145(98%)	129(92%)	
ULCER	0(0%)	0(0%)	0(0%)	3(2%)	11(8%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	143(41/102)	100(32/68)	88(20/68)	89(22/67)	93(34/59)	
CRUDE EROSION/ULCER RATE:						<0.001
NO EROSION/ULCER	99(95%)	147(93%)	145(96%)	140(95%)	111(79%)	
EROSION/ULCER (c)	5(5%)	11(7%)	6(4%)	8(5%)	29(21%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	143(41/102)	100(32/68)	88(20/68)	89(22/67)	93(34/59)	
FINAL						
CRUDE ULCER RATE (b):						<0.001
NO ULCER	217(100%)	232(100%)	227(100%)	218(99%)	199(95%)	
ULCER	0(0%)	0(0%)	0(0%)	3(1%)	11(5%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(29/1)	26(26/0)	12(12/0)	16(16/0)	23(23/0)	
CRUDE EROSION/ULCER RATE:						<0.001
NO EROSION/ULCER	206(95%)	213(92%)	215(95%)	212(96%)	174(83%)	
EROSION/ULCER (c)	11(5%)	19(8%)	12(5%)	9(4%)	36(17%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(29/1)	26(26/0)	12(12/0)	16(16/0)	23(23/0)	

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. 50MG BID	100MG BID VS. 50MG BID	200MG BID VS. 100MG BID	200MG BID VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS.
WEEK 12										
ULCER RATE:	#	0.218	#	#	0.079	0.142	0.004	<0.001	<0.001	0.012
EROSION/ ULCER RATE:	0.885	0.487	0.629	0.320	0.992	0.533	<0.001	<0.001	<0.001	<0.001
FINAL										
ULCER RATE:	#	0.153	#	#	0.098	0.136	<0.001	<0.001	<0.001	0.016
EROSION/ ULCER RATE:	0.632	0.756	0.106	0.246	0.160	0.599	<0.001	0.002	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;
Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient

(c). Erosion/ Ulcer is defined as an endoscopy score equal to 3,4,5,6,7
(d) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
(e) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
P- value is not calculable

Reviewer's Comment: In study N49- 96- 02- 021, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with all other treatment groups ($p \leq 0.05$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p > 0.05$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.05$).

Study N49-98-06-062

Study Design

This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving naproxen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8 and 12 weeks after the first dose of study medication. Endoscopies were performed pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria were randomly assigned to receive either SC-58635 200 mg BID or naproxen 500 mg BID for 12 weeks.

STUDY OBJECTIVES

Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcer associated with SC-58635 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

UGI ENDOSCOPY AND ARTHRITIS EFFICACY RESULTS

Data Sets Analyzed

All randomized patients who received at least one dose of study medication (n=536) were included in the Endoscopy and Arthritis Efficacy ITT Cohorts.

Counts of gastroduodenal ulcers by treatment group and observation time are presented in Table 3.7. Crude ulcer rates are presented in Table 3.8. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportion of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 18 (9%) SC-58635 200 mg BID patients and 87 (41%) naproxen 500 mg BID patients. These results were confirmed by analysis of Final Visit endoscopies that included all patients who had endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis 20 (8%) SC-58635 200 mg BID patients and 89 (35%) naproxen 500 mg BID patients developed a gastroduodenal ulcer over the course of the study and this difference was statistically significant ($p<0.001$) (Table 3.8).

TABLE 3.7 GASTRODUODENAL ENDOSCOPY RESULTS-- N49- 97- 02- 062
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

		SC- 58635 200MG BID (N= 269)		NAPROXEN 500MG BID (N= 267)	
STUDY	DAYS	NO ULCER	ULCER	NO ULCER	ULCER
	2-20	12	3	6	3
WEEK 4	(21-35)	242	7	200	44
	36-48	6	0	7	0
WEEK 8	(49-63)	222	5	156	26
	64-76	2	0	1	0
WEEK 12	(77-91)	193	3	127	14
	>91	7	2	3	2

TABLE 3.8 GASTRODUODENAL ENDOSCOPY RESULTS-- N49- 97- 02- 062
ANALYSIS OF CRUDE ULCER RATE-ITT

	SC-58635 200MG BID (N=269)	NAPROXEN 500MG BID (N=267)	p-VALUE(c)
WEEK 0-4			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	242(96%)	200(81%)	
ULCER	10(4%)	47(19%)	
UNKNOWN(WITHOUT & WITH ENDO)	17(5/12)	20(14/6)	
WEEK 0-8			
CRUDE ULCER RATE(a)			<0.001
NO ULCER	222(94%)	156(68%)	
ULCER	15(6%)	73(32%)	
UNKNOWN(WITHOUT & WITH ENDO)	32(3/29)	38(10/28)	
WEEK 0-12			
CRUDE ULCER RATE(a)			<0.001
NO ULCER	193(91%)	127(59%)	
ULCER	18(9%)	87(41%)	
UNKNOWN(WITHOUT & WITH ENDO)	58(3/55)	53(10/43)	
WEEK 0-FINAL(b)			
CRUDE ULCER RATE(a)			<0.001
NO ULCER	246(92%)	168(65%)	
ULCER	20(8%)	89(35%)	
UNKNOWN(WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of gastric ulcers by treatment group and observation time are presented in Table 3.9. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.10. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 12 (6%) SC-58635 200 mg BID patients and 74 (37%) naproxen 500 mg BID patients. These results were confirmed by analyses of Final Visit endoscopies that included all patients who had an endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis 13 (5%) SC-58635 200 mg BID patients compared to 76 (30%) naproxen 500 mg BID patients developed an ulcer and this difference was statistically significant ($p<0.001$). The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and naproxen groups being statistically significant ($p<0.001$).

TABLE 3.9 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 062
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=269)		NAPROXEN 500MG BID (N=267)	
STUDY DAYS	NOULCER	ULCER	NOULCER	ULCER
2-20	14	1	8	1
WEEK 4 (21-35)	243	6	206	38
36-48	6	0	7	0
WEEK 8 (49-63)	225	2	160	22
64-76	2	0	1	0
WEEK 12 (77-91)	193	3	128	13
>91	8	1	3	2

TABLE 3.10 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 062
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635 200MG BID (N=269)	NAPROXEN 500MG BID (N=267)	p-VALUE(d)
WEEK 0-12			
CRUDE ULCER RATE (a)		<0.001	
NO ULCER	193(94%)	128(63%)	
ULCER	12(6%)	74(37%)	
UNKNOWN (WITHOUT & WITH ENDO)	64(3/61)	65(10/55)	
CRUDE EROSION/ULCER RATE (b)			<0.001
NO EROSION/ULCER	162(79%)	65(32%)	
EROSION/ULCER	43(21%)	137(68%)	
UNKNOWN (WITHOUT & WITH ENDO)	64(3/61)	65(10/55)	
WEEK 0-FINAL (c)			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	253(95%)	181(70%)	
ULCER	13(5%)	76(30%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	
CRUDE EROSION/ULCER RATE (b)			<0.001
NO EROSION/ULCER	180(68%)	59(23%)	
EROSION/ULCER	86(32%)	198(77%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of duodenal ulcers by treatment group and observation time are presented in Table 3.11. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.12. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference (p=0.002). Ulcers developed in 8 (4%) SC-58635 200 mg BID patients and 19 (12%) naproxen 500 mg BID patients. These results were confirmed by analyses of Final Visit endoscopies that included all patients who had an endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis, 9 (3%) SC-58635 200 mg BID patients compared to 19 (7%) naproxen 500 mg BID patients developed an ulcer and this difference was statistically significant (p=0.030). The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and naproxen groups being statistically significant (p=0.017).

TABLE 3.11 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 062
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=269)		NAPROXEN 500MG BID (N=267)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER
2-20	13	2	6	3
WEEK 4 (21-35)	247	2	234	10
36-48	6	0	7	0
WEEK 8 (49-63)	224	3	177	5
64-76	2	0	2	0
WEEK 12 (77-91)	195	1	140	1
>91	8	1	5	0

TABLE 3.12 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 062
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635 200MG BID (N=269)	NAPROXEN 500MG BID (N=267)	p-VALUE(d)
WEEK 0-12			
CRUDE ULCER RATE (a)			0.002
NO ULCER	195(96%)	139(88%)	
ULCER	8(4%)	19(12%)	
UNKNOWN (WITHOUT & WITH ENDO)	66(3/63)	109(10/99)	
CRUDE EROSION/ULCER RATE (b)			0.017
NO EROSION/ULCER	176(87%)	125(79%)	
EROSION/ULCER	27(13%)	33(21%)	
UNKNOWN (WITHOUT & WITH ENDO)	66(3/63)	109(10/99)	
WEEK 0-FINAL (c)			
CRUDE ULCER RATE (a)			0.030
NO ULCER	257(97%)	238(93%)	
ULCER	9(3%)	19(7%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	
CRUDE EROSION/ULCER RATE (b)			<0.001
NO EROSION/ULCER	222(83%)	173(67%)	
EROSION/ULCER	44(17%)	84(33%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Reviewer's Comment: In study N49- 97- 02- 062, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with the SC-58635 group ($p \leq 0.05$).

Study N49- 97- 02- 071

Study Design

This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving diclofenac or ibuprofen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8, and 12 weeks after the first dose of study medication. Endoscopies were performed Pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria were

randomly assigned to receive SC-58635 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID for 12 weeks.

STUDY OBJECTIVES

Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcers associated with SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Counts of patients with gastroduodenal ulcers by treatment group and observation time are presented in Table 3.13. Crude ulcer rates are presented in Table 3.14. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportion of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 25 (9%) SC-58635 200 mg BID patients, 36 (12%) diclofenac 75 mg BID patients, and 78 (28%) ibuprofen 800 mg TID patients. Pairwise comparisons indicated these differences were statistically significant for the SC-58635 200 mg BID group compared to the ibuprofen 800 mg TID group and for the diclofenac group compared to the ibuprofen group ($p<0.001$). These results were confirmed by analysis of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis, 25 (7%) SC-58635 200 mg BID patients, 36 (10%) diclofenac 75 mg BID patients, and 78 (23%) ibuprofen 800 mg TID patients developed a gastroduodenal ulcer over the course of the study. Pairwise comparisons indicated a statistically significant difference for the SC-58635 treatment group compared to the ibuprofen group and the diclofenac group compared to the ibuprofen group ($p<0.001$) (Table 3.14).

TABLE 3.13 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=365)		DICLOFENAC 75MG BID (N=387)		IBUPROFEN 800MG TID (N=345)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
2-20	9	0	12	0	8	2
WEEK 4 (21-35)	324	13	332	18	281	40
36-48	14	1	10	1	7	1
WEEK 8 (49-63)	289	6	296	9	226	14
64-76	13	1	10	1	13	1
WEEK 12 (77-91)	269	4	270	7	198	20
>91	6	0	4	0	2	0

TABLE 3.14 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071
ANALYSIS OF CRUDE ULCER RATE-ITT

	SC-58635 200MG BID (N=365)	DICLOFENAC 75MG BID (N=387)	IBUPROFEN 800MG TID (N=345)	OVERALL p-VALUE(c)	SC-58635 VS DICLOFENAC p-VALUE(c)	SC-58635 VS IBUPROFEN p-VALUE(c)	DICLOFENAC VS IBUPROFEN p-VALUE(c)
WEEK 0-4							
CRUDE ULCER RATE (a)				<0.001	0.370	<0.001	<0.001
NO ULCER	324(96%)	332(95%)	281(87%)				
ULCER	13(4%)	18(5%)	42(13%)				
UNKNOWN(WITHOUT & WITH ENDO)	28(19/9)	37(25/12)	22(15/7)				
WEEK 0-8							
CRUDE ULCER RATE (a)				<0.001	0.220	<0.001	<0.001
NO ULCER	289(94%)	296(91%)	226(80%)				
ULCER	20(6%)	28(9%)	57(20%)				
UNKNOWN(WITHOUT & WITH ENDO)	56(9/47)	63(15/48)	62(12/50)				
WEEK 0-12							
CRUDE ULCER RATE (a)				<0.001	0.138	<0.001	<0.001
NO ULCER	269(91%)	270(88%)	198(72%)				
ULCER	25(9%)	36(12%)	78(28%)				
UNKNOWN(WITHOUT & WITH ENDO)	71(9/62)	81(15/66)	69(11/58)				
WEEK 0-FINAL (b)							
CRUDE ULCER RATE (a)				<0.001	0.123	<0.001	<0.001
NO ULCER	331(93%)	336(90%)	256(77%)				
ULCER	25(7%)	36(10%)	78(23%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of patients with gastric ulcers by treatment group and observation time are presented in Table 3.15. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.16. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 23 (8%) SC-58635 200 mg BID patients, 27 (9%) diclofenac 75 mg BID patients and 60 (23%) ibuprofen 800 mg TID patients and this difference was statistically significant for the SC-58635 group compared to the ibuprofen group and for the diclofenac group compared to the ibuprofen group ($p<0.001$). These results were confirmed by analyses of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis, 23 (6%) SC-58635 200 mg BID patients compared to 27 (7%) diclofenac 75 mg BID patients and 60 (18%) ibuprofen 800 mg TID patients developed an ulcer and this difference was statistically significant for the SC-58635 group compared to the ibuprofen group as well as the diclofenac group compared to the ibuprofen group ($p<0.001$).

The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and ibuprofen group and the difference between the diclofenac and ibuprofen group being statistically significant ($p<0.001$).

TABLE 3.15 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 071
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635		DICLOFENAC		IBUPROFEN	
	200MG BID		75MG BID		800MG TID	
	(N=365)		(N=387)		(N=345)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
2-20	9	0	12	0	8	2
WEEK 4 (21-35)	325	12	336	14	294	27
36-48	14	1	10	1	7	1
WEEK 8 (49-63)	290	5	299	7	230	10
64-76	13	1	10	1	13	1
WEEK 12 (77-91)	270	4	274	4	199	19
>91	6	0	4	0	2	0

TABLE 3.16 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 071
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635	DICLOFENAC	IBUPROFEN		SC-58635 VS	SC-58635 VS	DICLOFENAC VS
	200MG BID	75MG BID	800MG TID	OVERALL	DICLOFENAC	IBUPROFEN	IBUPROFEN
	(N=365)	(N=387)	(N=345)	p-VALUE(d)	p-VALUE(d)	p-VALUE(d)	p-VALUE(d)
WEEK 0-12							
CRUDE ULCER RATE(a)				<0.001	0.515	<0.001	<0.001
NO ULCER	270(92%)	274(91%)	199(77%)				
ULCER	23(8%)	27(9%)	60(23%)				
UNKNOWN(WITHOUT & WITH ENDO)	72(9/63)	86(15/71)	86(11/75)				
CRUDE EROSION/ULCER RATE(b)				<0.001	0.224	<0.001	<0.001
NO EROSION/ULCER	226(77%)	223(74%)	117(45%)				
EROSION/ULCER	67(23%)	78(26%)	142(55%)				
UNKNOWN(WITHOUT & WITH ENDO)	72(9/63)	86(15/71)	86(11/75)				
WEEK 0-FINAL (c)							
CRUDE ULCER RATE				<0.001	0.534	<0.001	<0.001
NO ULCER	333(94%)	345(93%)	274(82%)				
ULCER	23(6%)	27(7%)	60(18%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				
CRUDE EROSION/ULCER RATE				<0.001	0.426	<0.001	<0.001
NO EROSION/ULCER	221(62%)	228(61%)	105(31%)				
EROSION/ULCER	135(38%)	144(39%)	229(69%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient for crude ulcer rate and based on the highest score for each patient during treatment for crude erosion/ ulcer rate.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of patients with duodenal ulcers by treatment group and observation time are presented in Table 3.17. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.18. Over the 12 weeks of the study, for patients with know ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 3 (1%) SC-58635 200 mg BID patients, 14 (5%) diclofenac 75 mg BID patients, and 22 (9%) ibuprofen 800 mg TID patients and these differences were statistically significant for the SC-58635 group compared to the ibuprofen group ($p<0.001$), and for the SC-58635 group compared to the diclofenac group ($p=0.007$). These results were confirmed by analyses of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis 3 (<1%) SC-58635 200 mg BID patients compared to 14

(4%) diclofenac 75 mg BID patients and 22 (7%) ibuprofen 800 mg TID patients developed an ulcer and these differences were statistically significant for the SC-58635 group compared to the ibuprofen group ($p<0.001$) and for the SC-58635 group compared to the diclofenac group ($p=0.008$).

The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the differences between the SC-58635 and ibuprofen groups and the SC-58635 and diclofenac groups and the diclofenac and ibuprofen groups being statistically significant at 0-Week 12 ($p\leq 0.015$).

TABLE 3.17 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635		DICLOFENAC		IBUPROFEN	
	200MGBID		75MGBID		800MGTID	
	(N=365)		(N=387)		(N=345)	
STUDYDAYS	NOULCER	ULCER	NOULCER	ULCER	NOULCER	ULCER
2-20	9	0	12	0	10	0
WEEK4(21-35)	336	1	342	8	305	16
36-48	15	0	11	0	8	0
WEEK8(49-63)	294	1	303	2	236	4
64-76	14	0	11	0	14	0
WEEK12(77-91)	272	1	273	4	216	2
>91	6	0	4	0	2	0

TABLE 3.18 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635	DICLOFENAC	IBUPROFEN		SC-58635 VS	SC-58635 VS	DICLOFENAC VS
	200MG BID	75MG BID	800MG TID	OVERALL	DICLOFENAC	IBUPROFEN	IBUPROFEN
	(N=365)	(N=387)	(N=345)	p-VALUE(d)	p-VALUE(d)	p-VALUE(d)	p-VALUE(d)
WEEK 0-12							
CRUDE ULCER RATE(a)				<0.001	0.007	<0.001	0.055
NO ULCER	272(99%)	273(95%)	216(91%)				
ULCER	3(1%)	14(5%)	22(9%)				
UNKNOWN(WITHOUT & WITH ENDO)	90(9/81)	100(15/85)	107(11/96)				
CRUDE EROSION/ULCER RATE(b)				<0.001	0.003	<0.001	0.015
NOEROSION/ULCER	258(94%)	252(88%)	191(80%)				
EROSION/ULCER	17(6%)	35(12%)	47(20%)				
UNKNOWN(WITHOUT & WITH ENDO)	90(9/81)	100(15/85)	107(11/96)				
WEEK 0-FINAL(c)							
CRUDE ULCER RATE				<0.001	0.008	<0.001	0.093
NO ULCER	353(99%)	358(96%)	312(93%)				
ULCER	3(<1%)	14(4%)	22(7%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				
CRUDE EROSION/ULCE RRATE				<0.001	0.006	<0.001	0.008
NO EROSION/ULCER	314(88%)	307(83%)	248(74%)				
EROSION/ULCER	42(12%)	65(17%)	86(26%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient for crude ulcer rate and based on the highest score for each patient during treatment for crude erosion/ ulcer rate.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Reviewer's Comment: In study N49- 97- 02- 071, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group to be significantly greater compared with the SC-58635 group and the diclofenac group ($p \leq 0.05$). There was no difference in the incidence of gastroduodenal and gastric ulcers

in the SC-58635 group and the diclofenac group ($p>0.05$). The incidence of duodenal ulcers in the diclofenac group was significantly greater compared with the SC-58635 group ($p \leq 0.05$).

There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p>0.05$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.05$).

4. Integrated safety:

12 week studies

The 12-week studies and the 6-week studies were pooled separately for the safety analysis. The results are listed in Tables 4.1-4.8. The frequencies of reported adverse events are listed by body system and treatment groups. Individual adverse events within a certain body system are listed (in italic) if the p-value for the differences among treatment groups were ≤ 0.05 and the percentage for at least one of the treatment groups exceeds 1%. The p-values were from the Mantel-Haenszel chi-square test. Since the Mantel-Haenszel chi-square test is only asymptotically reliable, and the frequencies of reported adverse events are usually low, caution should be exercised while interpreting these p-values.

Table 4.1 lists the frequencies of all reported adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Gastro-intestinal system, skin and appendages. Within "body as a whole", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): Dema Peripheral, allergic reaction, and chest pain. Within "General and peripheral nervous system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): headache. Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): Abdominal pain, constipation, dyspepsia, flatulence, vomiting. Within "Musculo-skeletol system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): arthralgia. Within "skin and appendages", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): rash. Within "urinary system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): micturition frequency.